1. Claims 1-7 are enabled under 35 USC §112, first paragraph.

Claims 1-7 remain rejected as lacking enablement. In the Advisory Action it is stated that the rejection is maintained for the reasons of record. This rejection is respectfully traversed.

In the Final Office Action, mailed May 22, 1998, and in the Advisory Action, the Examiner indicated that claims directed to a method of decreasing inflammation caused by ischemia comprising administering heparinase is allowable, however, also in the Advisory Action, the Examiner states that administration of heparanase "to decrease inflammatory processes mediated by different cytokines and infiltrating cells" is not considered to be enabled.

Applicants submit that a fundamental point of Applicants' claimed invention, namely the process by which all localized inflammation occurs, is not being recognized by the Examiner. The following is an explanation of this fundamental point, and is supported in Applicants' specification, at least at pages 8-9, 13-15 and the Examples on pp. 24-et seq. The teachings of Applicants specification were reaffirmed in Luster, see at least page 436, first col., first paragraph, page 438-439, bridging paragraph, and Figure 2 on page 440. A copy of Luster, A. D., 1998, *New Engl. J. Med.*, 338:436-445 ("Luster") was submitted together with the response to the final Office Action and is being attached hereto for the Examiner's convenience[1].

The fundamental point which is being overlooked is as follows. All localized inflammation is controlled by chemokines (which are chemotactic cytokines). Further, all chemokines are bound to the cell surface by the molecules heparin and heparan sulfate. More specifically, Chemokines are secreted at the sites of

[1]Applicants would be pleased to submit the Luster review article with a Rule 1.132 Declaration if the Examiner would deem it appropriate.

inflammation by the damaged tissue, the secreted chemokines move to the vascular lumen and are locally retained on the surface of the vascular endothelial cells by being bound to the heparan sulfate and heparin components of proteoglycan surface proteins present on the surface of all vascular endothelial cells (Luster, Figure 2 and figure legend). The binding of the chemokines by heparin and heparan sulfate groups establishes a localized chemokine concentration gradient which is recognized by leukocytes (the bodys' tissue infiltrating cells) which are naturally present in the blood and are constantly circulating through the vascular lumen. Leukocytes are comprised of specific cells, including neutrophils, eosimophils and monocytes. Finally, the presence of the chemokine gradient activates the leukocytes which leads to leukocyte adherence to the endothelial cells that have bound the cytokines. The adhered leukocytes extravasate from the vascular lumen at the site of binding to the cytokines and infiltrate the damaged tissue. Therefore, as is taught in both Applicants' specification and reaffirmed by Luster, chemokines, including chemokines which cause inflammation at the site of an ischemia reperfusion injury and all "other" chemokines, induce localized inflammation through their being bound to the endothelial cell surfaces in the lumen by heparan sulfate and heparin.

Thus, based upon the teachings of Applicants specification, one of ordinary skill in the art would expect that the removal of chemokines (whether they are chemokines that are present due to ischemia or "other" chemokines) from the endothelial cell surfaces of the lumen by digestion of heparan sulfate and heparin with heparinase enzyme, as claimed in the instant claims, would result in the decrease of a localized inflammatory response regardless of which chemokine and infiltrating cells are specifically responsible for the inflammation at that site.

Based on the foregoing remarks, the Examiner is respectfully requested to reconsider and withdraw this rejection of claims 1-7.

2. The claims are patentable under 35 USC § 103 in view of the cited art.

Claims 1-7 remain rejected under 35 USC §103(a) as being unpatentable. In the Advisory Action, the Examiner notes that Rule 1.131 Declaration is sufficient to establish that the invention was conceived and reduced to practice prior to the publication of Hoogewerf et al., Gilat et al. (J. Exp. Med.), Lider et al. and Gilat et al. (J. Immunol.). Also in the Advisory Action, the Examiner states that the rejection over Vlodavsky et al., Zimmerman et al. (U.S. 5,169,772), Fuks et al. (U.S. 5,362,641), and Sasisekharan et al. (U.S. 5,567,417) in view of Ratner et al. would be maintained "since the remaining cited art teaches a method of decreasing localized inflammatory responses by administering heparinase." This rejection is respectfully traversed.

Each of the cited articles will be discussed in turn and then their combined teachings will be discussed below.

Vlodavsky et al. teaches that platelet heparitinase is an enzyme which hydrolyzes heparan sulfate and heparin. This document does not teach or suggest the use of heparinase enzyme to decrease a localized inflammatory response, in fact this document does not provide a suggestion of any use of heparinase enzyme.

The '772 patent teaches a large scale method for the purification of heparinase from *Flavobacterium heparinum*. This document does not teach or suggest the use of heparinase enzyme to decrease a localized inflammatory response.

The '641 patent teaches a use of heparinase enzyme to release angiogenic endothelial cell factors from basement membranes and subendothelial extracellular matrix ("ECM") (col. 2, lines 63-66). As discussed in col. 3 lines 1-25, angiogenic factors promote "angiogenesis" which is the process of formation of new blood vessels (also known as "neovascularization") which accompanies a number of normal and abnormal processes in the body, such as the processes of tumor formation and

wound healing. As discussed in col. 3, lines 28-64, fibroblast growth factor ("FGF") and endothelial cell growth factor ("ECGF") are two angiogenic factors which have been determined to bind heparin with high affinity, and are demonstrated to be bound to the ECM. The role of FGF in wound healing in further discussed in col. 4, especially at lines 37-45, and FGF is stated to be believed to play a significant role in the process of wound healing. Further, in col. 4, lines 55-57, it is suggested that administration of heparanase would release the ECM-bound FGF and thus promote the wound healing process. Finally, it is also suggested, in col. 4, line 66 through col. 5, line 6, that

> "Pathological conditions other than wound healing, which are likely to benefit from neovascularization promoted by FGF include cardiac, cerebral and peripheral ischemic diseases and diseases associated with vascular damage, such as diabetes, hypertension and systemic lupus erythematosus. Other potential clinical applications for angiogenic factors are processes such as ovulation, hair growth, transplantation, nerve regeneration and bone and cartilage repair. "

As one of ordinary skill in the art would be aware, however, growth factors and chemokines are distinctly <u>different</u> classes of molecules, which classes are co-exclusive of one another as these molecules do not have the same functions in the body. Contrary to the assertion in the Advisory Action and on page 5 of the final Office Action, the '641 patent <u>does not</u> teach use of heparinase enzyme to decrease a localized inflammatory response, but rather teaches that heparinase enzymes may be useful to release the angiogenic growth factor FGF from the ECM and thus <u>promote neovascularization</u> which in turn would be beneficial in one or more clinical applications. As one of ordinary skill in the art would be aware, however, neovascularization is <u>not</u> an aspect of decreasing a localized inflammatory response. Thus, a teaching that administration of heparanase enzyme is useful to promote neovascularization <u>does not suggest</u> that administration of heparinase enzyme would be useful to decrease localized inflammation.

The '417 patent, in direct contradiction of the '641 patent, teaches that administration of heparinase enzymes are useful to inhibit angiogenesis (rather than promote angiogenesis) (see, col. 4, lines 6-14). Several disease conditions that are associated with neovascularization are listed in col. 1, line 59 through col. 2, line 4, which disease conditions could be treated by inhibition of neovascularization. As one of ordinary skill in the art would be aware, however, inhibition of neovascularization is not an aspect of decreasing a localized inflammatory response. Thus a teaching that administration of heparanase enzyme is useful to inhibit neovascularization does not suggest that administration of heparinase enzyme would be useful to decrease localized inflammation.

Ratner et al., as stated in the response to the final Office Action, *teaches away* from the claimed invention. As taught in the instant specification, the movement of T cells (leukocytes) through the basement membrane is a cause of the localized inflammatory response. Ratner et al. teaches that administration of heparanases leads to T cell movement through the basement membrane (pg. 82), thus incorrectly suggesting to one of skill in the art that administration of heparanase enzymes would increase the inflammatory response rather than decrease the inflammatory response. Therefore, Ratner et al. teaches away from the claimed invention.

As discussed above, not one of the cited references teaches or suggests the use of heparinase enzymes to decrease a localized inflammatory response. Further, as one of ordinary skill in the art would be aware, neither the promotion nor the inhibition of neovascularization is an aspect of decreasing a localized inflammatory response. Thus the combined teachings of the primary and secondary references do not teach or suggest the claimed invention and therefore do not make the claimed invention obvious.

Based on the foregoing remarks, the Examiner is respectfully requested to reconsider and withdraw this rejection of claims 1-7.

Summary

Reconsideration of the application in view of the foregoing remarks is respectfully requested. The amended application should be in condition for allowance, and such action is respectfully requested.

Respectfully submitted,
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